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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/653,114	05/24/1996	ERIK S FALCK-PEDERSEN	19603/233(CR	5761

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	48

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/653,114	Applicant(s) Falck-Pedersen
	Examiner Richard Schnizer	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 5, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 4, 9, and 17-22* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 4, 9, and 17-22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *May 24, 1996* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment, filed 5/5/03, has been entered as Paper No. 47.

Claims 1, 3, 4, 9, and 17-22 are pending and under consideration in this Office Action.

Applicant's amendment to the abstract is sufficient to overcome the objection set forth in the previous Office Action.

Claim Rejections - 35 USC § 103

Claims 1, 9, and 17-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al in view of Huang *et al.*, and Choi *et al.*

Schneider teaches an adenoviral vector comprising a herpes virus thymidine kinase promoter inserted into E3, and oriented oppositely to the direction of transcription of E3. See abstract. The vector comprises insertion sites for heterologous genes. See Fig. 1(a) on page 419 which shows that the vector contains a Bam HI site that can be used to place a heterologous gene under the control of the promoter, as well as a Pvu II restriction site that can be used for this purpose. The vector also contains the herpes virus thymidine kinase polyadenylation signal downstream of the Bam HI site. See page 418, lines 5-7 of paragraph 7, and Fig. 1(a) on page 419. Schneider also teaches an adenoviral vector comprising a heterologous gene, and a method of expressing the gene in a host cell. See page 420, first paragraph.

Schneider does not teach splice acceptor and donor signals positioned between the insertion site and the promoter.

Huang teaches that including an intron in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2).

Choi teaches that incorporation of a generic intron between a promoter and a gene of interest causes 5- to 300-fold increases in transgene expression in mice. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector of Schneider by including the intron of either Huang or Choi. One would have been motivated to do so with the reasonable expectation that inclusion of the intron would result in a vector providing improved gene expression.

Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Huang, and Choi as applied to claims 1, 9, and 17-19, 21, and 22, above, and further in view of Fang et al (Hepatology (1989) 10(5): 781-787).

The teachings of Schneider, Huang, and Choi are summarized above and can be combined to render obvious an adenoviral vector comprising an expression cassette containing a herpes simplex virus thymidine kinase promoter, an intron, a gene insertion site, and a polyadenylation signal, wherein the expression cassette is oriented oppositely to the direction of transcription of the adenoviral E3 region.

These references do not teach a vector containing the mouse CMV promoter.

Fang teaches that the mouse CMV promoter is more active than the herpes simplex virus thymidine kinase promoter.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the mouse CMV promoter of Fang for the tk promoter of Schneider because Fang teaches that the CMV promoter is more active than the tk promoter, so one could have reasonably expected improved expression.

Thus the invention as a whole was prima facie obvious.

Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Huang, and Choi as applied to claims 1, 9, and 17-19, 21, and 22, above, and further in view of Kaufman (US Patent 4,740,461, issued 4/26/88).

The teachings of Schneider, Huang, and Choi are summarized above and can be combined to render obvious an adenoviral vector comprising an expression cassette containing a herpes simplex virus thymidine kinase promoter, an intron, a gene insertion site, and a herpes simplex virus thymidine kinase polyadenylation signal, wherein the expression cassette is oriented oppositely to the direction of transcription of the adenoviral E3 region.

These references do not teach a vector containing the mouse beta globin polyadenylation signal.

Kaufman teaches expression vectors for eukaryotic cells, noting that eukaryotic polyadenylation sites are well known and that "[e]xemplary polyadenylation sequences may be obtained from mouse beta-globin, simian virus 40 late or early region genes, etc." See column 8, lines 6-14. Thus Kaufman suggests the use of the mouse beta-globin polyadenylation site, and indicates that it is an art recognized equivalent to other polyadenylation sites.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the mouse beta-globin polyadenylation signal of Kaufman for the polyadenylation signal of Schneider because polyadenylation signals are art-recognized equivalents which perform the same function. MPEP 2144.06 indicates that it is obvious to substitute art-recognized equivalent components for each other, and an "express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Huang, and Choi as applied to claims 1, 9, and 17-19, 21, and 22, above, and further in view of Stratford-Perricaudet et al (1992).

The teachings of Schneider, Huang, and Choi are summarized above and can be combined to render obvious an adenoviral vector comprising an expression cassette containing a herpes simplex virus thymidine kinase promoter, an intron, a gene insertion site, and a polyadenylation

signal, wherein the expression cassette is oriented oppositely to the direction of transcription of the adenoviral E3 region.

These references do not teach a method of delivering a heterologous gene to an animal heart in vivo.

Stratford-Perricaudet teaches a method delivering a beta-galactosidase gene to an animal heart in vivo by use of an adenoviral vector. See abstract. The vector of Stratford-Perricaudet comprises a heterologous promoter and an insertion site for a heterologous gene. lacks an intron between the heterologous promoter and the heterologous gene insertion site. See Fig. 1 on page 627.

It would have been obvious to one of ordinary skill in the art at the time of the invention to insert the beta galactosidase gene of Stratford-Perricaudet into the expression vector of Schneider, Huang, and Choi, and to administer the vector to an animal heart in vivo as taught by Stratford-Perricaudet. One would have been motivated to do so because the vector of Schneider, Huang, and Choi comprises an intron between the promoter and the heterologous gene insertion site, and one could reasonably expect to obtain improved gene expression with this vector, in view of the teachings of Huang and Choi.

Thus the invention as a whole was prima facie obvious.

Claims 21 and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Huang, and Choi as applied to claims 1, 9, and 17-19, 21, and 22, above, and further in view of Fields (In Fundamental Virology, Raven Press, New York, 1990).

The teachings of Schneider, Huang, and Choi are summarized above and can be combined to render obvious an adenoviral vector comprising an expression cassette containing a herpes simplex virus thymidine kinase promoter, an intron, a gene insertion site, and a polyadenylation signal, wherein the expression cassette is oriented oppositely to the direction of transcription of the adenoviral E3 region.

These references are silent as to whether or not the expression cassette is oriented oppositely to the direction of transcription of the adenoviral E1 region.

Fields teaches that the adenoviral E1 and E3 regions are transcribed in the same direction, therefore the combined references must teach an adenoviral vector in which the expression cassette is oriented oppositely to the direction of transcription of the E1 region. See Fig. 11 on page 795 of Fields.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/5/03 have been fully considered but they are not persuasive. The essence of Applicant's argument is that Schneider teaches away from the claimed invention. Specifically, Applicant asserts in the paragraph bridging pages 4 and 5 of the response that the

"Schneider reference reports that detectable production of the VSV glycoprotein was *only* obtained from the adenoviral vector having TK-VSV insert in the *same orientation* as E3 transcription", relying for support on the abstract and page 420 second paragraph. The abstract indicates that while the TK promoter was functional in both orientations, expression of VSV from the expression construct oriented oppositely to E3 was not *readily* detectable. Emphasis added. Page 420, second full paragraph indicates that expression of VSV from the expression construct oriented oppositely to E3 was not detectable under certain experimental conditions. Applicant's attention is directed to page 422, last paragraph which clearly indicates that the reverse orientation construct was capable of expressing detectable amounts of VSV protein. Applicant's arguments that Schneider teaches away from the claimed invention are unpersuasive because the reverse orientation construct is clearly operable. The fact that the reverse orientation does not function as well as the parallel orientation is not sufficient to constitute "teaching away", Applicant's reliance on *In re Haruna* notwithstanding. Applicant is reminded that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to

the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.